DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 216

[Docket No. 98N–0655]

List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations to include a list of drug products that may not be used for pharmacy compounding under the exemptions under section 503A of the Federal Food, Drug, and Cosmetic Act (the act) because they have had their approval withdrawn or were removed from the market because the drug product or its components have been found to be unsafe or not effective. The list has been compiled under the new statutory requirements of the Food and Drug Administration Modernization Act of 1997 (Modernization Act).

DATES: This rule is effective on (*insert date 30 days after date of publication in the* **Federal Register**).

FOR FURTHER INFORMATION CONTACT: Wayne H. Mitchell, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041.

SUPPLEMENTARY INFORMATION:

I. Background

Section 127 of the Modernization Act (Pub. L. 105–115), which added section 503A to the act (21 U.S.C. 353a), describes the circumstances under which compounded drugs qualify for exemptions from certain adulteration, misbranding, and new drug provisions of the act (i.e., 501(a)(2)(B), 502(f)(1), and 505 of the act (21 U.S.C. 351(a)(2)(B), 352(f)(1), and 355)).

Section 503A of the act contains several conditions that must be satisfied for pharmacy compounding to qualify for the exemptions. Section 503A(b)(1)(C) of the act provides that the licensed pharmacist or licensed physician does not ''compound a drug product that appears on a list published by the Secretary in the **Federal Register** of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective.'' Section 503A(d)(1) of the act requires that the list of drug products that have been withdrawn or removed from the market because they were unsafe or not effective be issued as a regulation and that an advisory committee be consulted in the rulemaking process.

In the **Federal Register** of October 8, 1998 (63 FR 54082), FDA proposed a rule to establish the list of drug products that have been withdrawn or removed from the market because they were unsafe or not effective. The primary focus of that initial proposed rule and this final rule is on drug products that have been withdrawn or removed from the market because they were found to be unsafe. FDA may initiate rulemaking to add other drug products to the list that have been withdrawn or removed from the market because they were found to be not effective or to update the list as new information becomes available to the agency regarding products that were removed from the market because they were unsafe. The proposed rule was presented to the Pharmacy Compounding Advisory Committee at a meeting held on October 14 and 15, 1998 (see the **Federal Register** of September 4, 1998 (63 FR 47301)). The committee did not have any adverse comments on the proposed rule and did not suggest any changes.

II. Comments on the Proposed Rule

FDA received comments from consumers, pharmacists, a medical doctor, a pharmaceutical manufacturer, a pharmaceutical manufacturers' organization, and a committee representing the plaintiffs in a drug product liability class action suit.

1. Two comments questioned FDA's shortening the comment period from 75 to 45 days.

As FDA stated in the preamble to the proposed rule (63 FR 54082 at 54087 to 54088), the agency believes that a shorter comment period was warranted to expedite this rulemaking proceeding because the compounding of many of the drug products on the list would present a serious threat to the public health. Many of the drug products have caused death or life-threatening conditions. Some of the drugs on the list are believed to cause cancer, while others were shown to be toxic to the liver and other organs.

2. One comment objected to the wording of the first sentence of proposed § 216.24, which says "The following drug products were withdrawn or removed from the market because such drug products or components of such drug products were found to be unsafe or not effective." The comment expressed concerns that the finding that a drug was withdrawn from the market by the manufacturer because it was not safe or effective might be used in a product liability lawsuit against the manufacturer who voluntarily withdrew the drug product from the market. The comment also expressed concerns that fear of having the finding used against them might discourage manufacturers from voluntarily withdrawing drug products when concerns about the drug product's safety and effectiveness have developed.

The agency does not believe it is necessary to change the wording of § 216.24 in response to this comment. Compounding pharmacists and physicians are the intended audience for this rule. The purpose of § 216.24 is to provide these compounders a list of drugs that they may not compound under section 503A of the act. This list is not intended to be used as evidence in a product liability suit, and the addition of language designed to minimize the potential effect of the list in litigation is unnecessary to fulfill its intended purpose.

For the purposes of this rule, FDA has determined that it is not necessary to deviate from the statutory language found in section 503A(b)(1)(C) of the act, which prohibits compounders from compounding "a drug product that appears on a list published by [FDA] in the **Federal Register** of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or ineffective."

The agency wishes to emphasize that the inclusion of a drug product on the list does not mean that the drug product was marketed negligently, was defective, or was marketed in breach of any warranty. Even after exhaustive clinical studies, safety problems may not become apparent until a drug product has been in commercial distribution for a significant amount of time, so the fact that a drug was removed or withdrawn from the market does not mean that the drug was improperly placed in commercial distribution.

3. A large number of comments objected to drug products containing adrenal cortex being placed on the list. One of the comments included a photocopy of an article from the November issue of the magazine *Nutrition & Healing*. This article apparently is the source of much of the content of many of the comments. None of the comments provided any information about the removal of adrenal cortex extract from the market, other than the unsupported statements that the removal of adrenal cortex extract was economically motivated. These comments included unsupported statements that adrenal cortex extract has never been associated with a death or serious adverse event (except for a series of adverse events in 1996 and 1997 associated with contaminated adrenal cortex extract) and that adrenal cortex extract is safer and more effective than the synthetic adrenocortical steroids that have replaced it in medical use. The comments also asserted, without presenting any scientific data or historical information to support the assertion, that FDA acted improperly in directing the removal of drugs containing adrenal cortex from the market because the low levels of corticosteroids found in the drugs presented a substantial risk of undertreatment of serious conditions.

FDA's concerns about the safety of adrenal cortex extract have grown stronger since the drug product was removed from the market in 1978. Adrenal cortex extract is derived from the cortex adrenal glands of domestic food animals, including cattle. In 1986 the disease bovine spongiform encephalopathy (BSE) was identified in cattle. BSE has been found to be epidemic in Great Britain and present in Western Europe and Oman. Hundreds of thousands of cattle have either died or been destroyed as a result of BSE infection. Since that time strong evidence has been developed associating ingestion of tissues from BSE-infected cattle with the development of new variant Creutzfeldt–Jakob disease (nvCJD) in humans. A patient taking a drug derived from the adrenal cortex of a BSE-infected cow would be running an unacceptable risk of contracting nvCJD. Due to the destruction of BSE-infected cattle and other controls (see the **Federal Register** of August 29, 1994 (59 FR 44591)), the chances of a patient getting nvCJD from adrenal cortex extract are low. However, there is still a risk involved in taking adrenal cortex extract, and that risk must be taken very seriously in light of the fact that nvCJD appears to always be fatal.

Concerning the comments that FDA acted improperly in removing drugs containing adrenal cortex from the market because of a substantial risk of undertreatment of serious conditions, FDA's action was investigated by the General Accounting Office and found to be proper (see ''By the Comptroller General, Report to the Honorable Barry M. Goldwater, Jr., House of Representatives of the United States: Adrenal Cortical Extract Taken Off Drug Market'' (HRD–81–61, 1981)).

For the reasons stated previously, FDA is keeping drug products containing adrenal cortex on the list of drugs that may not be compounded under section 503A of the act.

4. One comment strongly supported the inclusion of drug products containing dexfenfluramine hydrochloride and fenfluramine hydrochloride on the list.

5. One comment pointed out that there is a hearing request pending before the agency regarding the withdrawal of approval of the applications for neomycin sulfate in sterile vials for injection (see the **Federal Register** of December 6, 1988 (53 FR 49232)) and another pending request for a hearing regarding the withdrawal of approval of the applications for neomycin sulfate

for prescription compounding (see the **Federal Register** of December 6, 1988 (53 FR 49231)). A petition for stay of action regarding the two actions mentioned above and regarding a labeling guideline for neomycin sulfate for prescription compounding (see the **Federal Register** of April 15, 1988 (53 FR 12662)) is also pending before the agency.

Because of the complex administrative record on neomycin sulfate currently before the agency and because of the public health need to expedite implementation of this rule, FDA is postponing final action on listing all parenteral drug products containing neomycin sulfate. Parenteral drug products containing neomycin sulfate may be added to the list at a later date.

III. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including having an annual effect on the economy of $100 million or adversely affecting in a material way a sector of the economy, competition, or jobs, or if it raises novel legal or policy issues. As discussed in the paragraphs below, the agency believes that this rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant

regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The agency has not estimated any compliance costs or loss of sales due to this final rule because it prohibits pharmacy compounding of only those drug products that have already been withdrawn or removed from the market. The agency is not aware of any routine use of these drug products in pharmacy compounding and received no significant data in response to the request in the preamble to the proposed rule for the submission of comments on this issue and current compounding usage data for these drug products. Additionally, FDA did not receive any comments on compliance costs and loss of sales due to this rule or current compounding usage data for the drug products listed in this rule at the Pharmacy Compounding Advisory Committee meeting held on October 14 and 15, 1998.

Unless an agency certifies that a rule will not have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options to minimize any significant economic impact of a regulation on small entities. The agency is taking this action in order to comply with section 503A of the act. This provision specifically directs the FDA to develop a list of drug products that have been withdrawn or removed from the market because such products or components have been found to be unsafe or not effective. Any drug product on this list will not qualify for the pharmacy compounding exemptions under section 503A of the act. The drug products on this list were manufactured by many different pharmaceutical firms, some of which may have qualified under the Small Business Administration (SBA) regulations (those with less than 750 employees) as small businesses. However, since the list only includes those drug products that have already been withdrawn or removed from the market for safety or efficacy concerns, this final rule will not negatively impact these small businesses. Moreover, no compliance costs are estimated for any of these small pharmaceutical firms because they are not the subject of this rule and are not expected to realize any loss of sales due to this rule. Further, the SBA guidelines limit the definition of small drug stores or

pharmacies to those that have less than $5.0 million in sales. Again, the pharmacies that qualify as small businesses are not expected to incur any compliance costs or loss of sales due to this regulation because the products have already been withdrawn or removed from the market, and the agency believes that these drugs would be compounded only very rarely, if ever. Therefore, FDA certifies that this rule will not have a significant economic impact on a substantial number of small entities.

Section 202 of the Unfunded Mandates Reform Act requires that agencies prepare an assessment of anticipated costs and benefits before it finalizes any rule requiring any expenditure by State, local, and tribal governments, in the aggregate, or by the private sector of $100 million (adjusted annually for inflation) in any 1 year. The publication of the list of products withdrawn or removed from the market because they were found to be unsafe or ineffective will not result in expenditures of funds by State, local, and tribal governments or the private sector in excess of $100 million annually. Because the agency does not estimate any annual expenditures due to the final rule, FDA is not required to perform a cost/benefit analysis according to the Unfunded Mandates Reform Act.

V. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

List of Subjects in 21 CFR Part 216

Drugs, Pharmacy compounding, Prescription drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 216 is added to read as follows:

PART 216—PHARMACY COMPOUNDING

Subpart A—General Provisions [Reserved]

Subpart B—Compounded Drug Products

Sec.

Authority: 21 U.S.C. 351, 352, 353a, 355, and 371.

Subpart A—General Provisions [Reserved]

Subpart B—Compounded Drug Products

§ 216.23 [Reserved]

§ 216.24 Drug products withdrawn or removed from the market for reasons of safety or effectiveness.

The following drug products were withdrawn or removed from the market because such drug products or components of such drug products were found to be unsafe or not effective. The following drug products may not be compounded under the exemptions provided by section 503A(a) of the Federal Food, Drug, and Cosmetic Act:

Adenosine phosphate: All drug products containing adenosine phosphate.

Adrenal cortex: All drug products containing adrenal cortex.

Azaribine: All drug products containing azaribine.

Benoxaprofen: All drug products containing benoxaprofen.

Bithionol: All drug products containing bithionol.

Bromfenac sodium: All drug products containing bromfenac sodium.

Butamben: All parenteral drug products containing butamben.

Camphorated oil: All drug products containing camphorated oil.

Carbetapentane citrate: All oral gel drug products containing carbetapentane citrate.

Casein, iodinated: All drug products containing iodinated casein.

Chlorhexidine gluconate: All tinctures of chlorhexidine gluconate formulated for use as a patient preoperative skin preparation.

Chlormadinone acetate: All drug products containing chlormadinone acetate.

Chloroform: All drug products containing chloroform.

Cobalt: All drug products containing cobalt salts (except radioactive forms of cobalt and its salts and cobalamin and its derivatives).

Dexfenfluramine hydrochloride: All drug products containing dexfenfluramine hydrochloride.

Diamthazole dihydrochloride: All drug products containing diamthazole dihydrochloride.

Dibromsalan: All drug products containing dibromsalan.

Diethylstilbestrol: All oral and parenteral drug products containing 25 milligrams or more of diethylstilbestrol per unit dose.

Dihydrostreptomycin sulfate: All drug products containing dihydrostreptomycin sulfate.

Dipyrone: All drug products containing dipyrone.

Encainide hydrochloride: All drug products containing encainide hydrochloride.

Fenfluramine hydrochloride: All drug products containing fenfluramine hydrochloride.

Flosequinan: All drug products containing flosequinan.

Gelatin: All intravenous drug products containing gelatin.

Glycerol, iodinated: All drug products containing iodinated glycerol.

Gonadotropin, chorionic: All drug products containing chorionic gonadotropins of animal origin.

Mepazine: All drug products containing mepazine hydrochloride or mepazine acetate.

Metabromsalan: All drug products containing metabromsalan.

Methamphetamine hydrochloride: All parenteral drug products containing methamphetamine hydrochloride.

Methapyrilene: All drug products containing methapyrilene.

Methopholine: All drug products containing methopholine.

Mibefradil dihydrochloride: All drug products containing mibefradil dihydrochloride.

Nitrofurazone: All drug products containing nitrofurazone (except topical drug products formulated for dermatalogic application).

Nomifensine maleate: All drug products containing nomifensine maleate.

Oxyphenisatin: All drug products containing oxyphenisatin.

Oxyphenisatin acetate: All drug products containing oxyphenisatin acetate.

Phenacetin: All drug products containing phenacetin.

Phenformin hydrochloride: All drug products containing phenformin hydrochloride.

Pipamazine: All drug products containing pipamazine.

Potassium arsenite: All drug products containing potassium arsenite.

Potassium chloride: All solid oral dosage form drug products containing potassium chloride that supply 100 milligrams or more of potassium per dosage unit (except for controlled-release dosage forms and those products formulated for preparation of solution prior to ingestion).

Povidone: All intravenous drug products containing povidone.

Reserpine: All oral dosage form drug products containing more than 1 milligram of reserpine.

Sparteine sulfate: All drug products containing sparteine sulfate.

Sulfadimethoxine: All drug products containing sulfadimethoxine.

Sulfathiazole: All drug products containing sulfathiazole (except those formulated for vaginal use).

Suprofen: All drug products containing suprofen (except ophthalmic solutions).

Sweet spirits of nitre: All drug products containing sweet spirits of nitre.

Temafloxacin hydrochloride: All drug products containing temafloxacin.

Terfenadine: All drug products containing terfenadine.

3,3′,4′,5-tetrachlorosalicylanilide: All drug products containing 3,3′,4′,5-tetrachlorosalicylanilide.

Tetracycline: All liquid oral drug products formulated for pediatric use containing tetracycline in a concentration greater than 25 milligrams/milliliter.

Ticrynafen: All drug products containing ticrynafen.

Tribromsalan: All drug products containing tribromsalan.

Trichloroethane: All aerosol drug products intended for inhalation containing trichloroethane.

Urethane: All drug products containing urethane.

Vinyl chloride: All aerosol drug products containing vinyl chloride.

Zirconium: All aerosol drug products containing zirconium.

Zomepirac sodium: All drug products containing zomepirac sodium.

Dated: March 4, 1999

March 1, 1999

William K. Hubbard
Acting Deputy Commissioner for
Policy

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